L64 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:303094 CAPLUS
DOCUMENT NUMBER: 129:66654
TITLE: Combinatorial blockade of calcineurin and CD28 signaling facilitates primary and secondary therapeutic gene transfer by adenovirus vectors in dystrophic (mdx) mouse muscles
AUTHOR(S): Guibinga, Ghiabe-Henri; Lochmuller, Hanns; Massie, Bernard; Nalbantoglu, Josephine; Karpati, George; Petrof, Basil J.
CORPORATE SOURCE: Department of Medicine, Royal Victoria Hospital, McGill University, Montreal, QC, H3A 1A1, Can.
SOURCE: Journal of Virology (**1998**), 72(6), 4601-4609
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recombinant adenovirus vectors (AdV) have been considered a potential vehicle for performing gene therapy in patients suffering from Duchenne muscular dystrophy but are limited by a cellular and humoral immune response that prevents long-term transgene expression as well as effective transduction after AdV readministration. Conventional immunosuppressive agents such as cyclosporine and **FK506**, which act by interfering with CD3-T-cell receptor-mediated signaling via calcineurin, are only partially effective in reversing these phenomena and may also produce substantial organ toxicity. We hypothesized that activation of redundant T-cell activation pathways could limit the effectiveness of these drugs at clin. tolerable doses. Therefore, we have tested the ability of immunomodulatory Igs (Ig) with different modes of action to facilitate AdV-mediated gene transfer to adult dystrophic (mdx) mice. When used in isolation, immunomodulatory Ig (anti-intercellular adhesion mol.-1, anti-leukocyte function-assocd. antigen-1, anti-CD2, and CTLA4Ig) were only mildly effective in mitigating cellular and/or humoral immunity against adenovirus capsid proteins and the therapeutic transgene product, dystrophin. However, the combination of **FK506** plus CTLA4Ig abrogated the immune response against adenovirus proteins and dystrophin to a degree not achievable with the use of either agent alone. At 30 days after AdV injection, >90% of myofibers could be found to express dystrophin with little or no evidence of a cellular immune response against transduced fibers. In addn., the humoral immune response was markedly suppressed, and this was assocd. with increased transduction efficiency following vector readministration. These data suggest that by facilitating both primary and secondary transduction after AdV administration, combined targeting of CD3-T-cell receptor-mediated signaling via calcineurin and the B7:CD28 costimulatory pathway could greatly increase the potential utility of AdV-mediated gene transfer as a therapeutic modality for genetic diseases such as Duchenne muscular dystrophy that will require long-term transgene expression and repeated vector delivery.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS

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L64 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:589213 CAPLUS
DOCUMENT NUMBER: 129:339616
TITLE: Adjusting immunosuppression to the identification of T-cell activating mediators in rejecting transplants: a novel approach to rejection diagnosis and treatment
AUTHOR(S): Strehlau, J.; Maslinski, W.; Chae, D.; Pavlakis, M.; Ehrich, J. H. H.; Strom, T. B.
CORPORATE SOURCE: Department of Medicine, Division of Immunology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
SOURCE: Transplantation Proceedings (**1998**), 30(5), 2389-2391
CODEN: TRPPA8; ISSN: 0041-1345
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors evaluated the differential effect of drugs on generation of mediators identified in rejecting grafts (IL-2, IL-7, IL-15, **CTLA -4**, granzyme B, perforin, FAS ligand) utilizing RT-PCR in IL-2, IL-7, IL-15 induced activation of peripheral blood mononuclear cells. Cyclosporine A, dexamethasone and **rapamycin** inhibitory effect on the prolipherative responce and gene expression was studied.

L64 ANSWER 12 OF 21 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999060961 MEDLINE
DOCUMENT NUMBER: 99060961 PubMed ID: 9846527
TITLE: Combined costimulation blockade plus **rapamycin** but not cyclosporine produces permanent engraftment.
AUTHOR: Li Y; Zheng X X; Li X C; Zand M S; Strom T B
CORPORATE SOURCE: Department of Medicine, Harvard Medical School, Beth Israel
Deaconess Medical Center, Boston, Massachusetts 02215, USA.
SOURCE: TRANSPLANTATION, **(1998 Nov 27)** 66 (10) 1387-8.
Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981229

AB BACKGROUND: Combined treatment of allograft recipients with anti-CD40 ligand and CTLA-4Ig (costimulation blockade) is a powerful promising albeit not consistently tolerizing therapy. It would be desirable to use an effective conventional immunosuppressive regimen in low doses or for a short course as an adjunct; however, cyclosporine treatment drastically blunts the ability of costimulation blockade to produce long-term engraftment. METHODS: Short courses of cyclosporine or **rapamycin** were compared as adjuncts to costimulation blockade in the murine BALB/c to C3H/He heterotopic cardiac allograft model. RESULTS: Although cyclosporine therapy blocked the capacity of costimulation blockade to produce permanent engraftment, combined **rapamycin** and costimulation blockade treatment produced permanent engraftment. CONCLUSION: A theoretical basis for the differing effects of cyclosporine and **rapamycin** upon the outcome of costimulation blockade is forwarded. Combined use of costimulation blockade and **rapamycin** may provide a means to bring costimulation blockade into the clinic.

L60 ANSWER 6 OF 14 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 94062014 MEDLINE
DOCUMENT NUMBER: 94062014 PubMed ID: 8242765
TITLE: The 4F9 antigen is a member of the tetra spans transmembrane protein family and functions as an accessory molecule in T cell activation and adhesion.
AUTHOR: Nojima Y; Hirose T; Tachibana K; Tanaka T; Shi L; Doshen J;
Freeman G J; Schlossman S F; Morimoto C
CORPORATE SOURCE: Division of Tumor Immunology, Dana-Farber Cancer Institute,
Boston, Massachusetts.
CONTRACT NUMBER: AI12609 (NIAID)
AI29530 (NIAID)
AR33713 (NIAMS)
SOURCE: CELLULAR IMMUNOLOGY, **(1993 Nov)** 152 (1) 249-60.
Journal code: 1246405. ISSN: 0008-8749.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19940201
Entered Medline: 19940106

AB In this report, we describe a 43- to 50-kDa protein, which may function as a costimulatory molecule for full activation of human T cells. This Ag, defined by a mouse monoclonal antibody (mAb) anti-4F9, is primarily distributed on "**helper**/inducer" or "memory" **CD4** +CD45RO+ subset. Like mAbs against many other accessory/costimulatory molecules, coimmobilization of anti-4F9 with anti-**CD3** resulted in synergistic T cell proliferation. In addition, immobilized anti-4F9 on plastic plates induced T cell spreading characterized by the development of prominent **dendritic** processes. A cDNA encoding the 4F9 Ag was isolated from a cDNA library constructed from PHA/PMA-activated T cells using a COS cell expression system. The sequence of the cDNA and a homology search revealed that the 4F9 Ag was identical to R2, a molecule recently cloned by subtractive hybridization. The 4F9/R2 Ag belongs to a newly identified supergene family (tetra spans transmembrane protein family) characterized by four putative transmembrane domains which are highly conserved between the members of this family. Based upon the phenotypical and functional studies described here, we propose that the 4F9 Ag is an integral membrane protein which can transmit signals involved in T cell proliferation and adhesion. The preferential distribution of this molecule on the CD4+CD45RO+ subset of T cells may contribute to the distinct activation profile and functional repertoire of these cells.

L73 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 95362832 MEDLINE
DOCUMENT NUMBER: 95362832 PubMed ID: 7543492
TITLE: **FK506** augments activation-induced programmed cell death of T lymphocytes in vivo.
AUTHOR: Migita K; Eguchi K; Kawabe Y; Tsukada T; Mizokami A; Nagataki S
CORPORATE SOURCE: First Department of Internal Medicine, Nagasaki University School of Medicine, Japan.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, **(1995 Aug)** 96 (2) 727-32.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19960129
Entered Medline: 19950911

AB **FK506** is an immunosuppressive drug that inhibits T cell receptor-mediated signal transduction. This drug can induce immunological tolerance in allograft recipients. In this study, we investigated the in vivo effects of **FK506** on T cell receptor-mediated apoptosis induction. Injection of anti-CD3 antibody (Ab) in mice resulted in the elimination of CD4+ **CD8**+ thymocytes by DNA fragmentation. **FK506** treatment significantly augmented thymic apoptosis induced by in vivo anti-CD3 Ab administration. Increased thymic apoptosis resulted in the disappearance of CD4+ **CD8**+ thymocytes after anti-CD3 Ab/ **FK506** treatment. DNA fragmentation triggered by **FK506** was induced exclusively in antigen-stimulated T cells, since enhanced DNA fragmentation induced by in vivo staphylococcal enterotoxin B (SEB) injection was confirmed in SEB-reactive V beta 8+ thymocytes but not in SEB-nonreactive V beta 6+ thymocytes. In addition to thymocytes, mature peripheral T cells also die by **activation-induced** programmed cell **death**. A similar effect of **FK506** on **activation-induced** programmed cell **death** was observed in SEB-activated peripheral spleen T cells. In contrast, cyclosporin A treatment did not enhance **activation-induced** programmed cell **death** of thymocytes and peripheral T cells. Apoptosis is required for the generation and maintenance of self-tolerance in the immune system. Our findings suggest that **FK506**-triggered apoptosis after elimination of antigen-activated T cells may represent a potential mechanism of the immunological tolerance achieved by **FK506** treatment.

L68 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:589613 CAPLUS
DOCUMENT NUMBER: 131:309663
TITLE: The role of the common cytokine receptor .gamma.-chain in regulating IL-2-dependent, activation-induced CD8+ T cell death
AUTHOR(S): Dai, Zhenhua; Arakeloy, Alexandr; Wagener, Maylene; Konieczny, Bogumila T.; Lakkis, Fadi G.
CORPORATE SOURCE: The Carlos and Marguerite Mason Transplantation Research Center, Renal Division, Department of Medicine, Veterans Affairs Medical Center and Emory University, Atlanta, GA, 30033, USA
SOURCE: Journal of Immunology (**1999**), 163(6), 3131-3137
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB IL-2-dependent, activation-induced T cell death (AICD) plays an important role in **peripheral tolerance**. Using CD8+ TCR-transgenic lymphocytes (2C), we investigated the mechanisms by which IL-2 preps. CD8+T cells for AICD. We found that both Fas and TNFR death pathways mediate the AICD of 2C cells. Neutralizing IL-2, IL-2R.alpha., or IL-2R.beta. inhibited AICD. In contrast, blocking the common cytokine receptor .gamma.-chain (.gamma.c) prevented Bcl-2 induction and augmented AICD. IL-2 up-regulated Fas ligand (FasL) and down-regulated .gamma.c expression on activated 2C cells in vitro and in vivo. Adult IL-2 gene-knockout mice displayed exaggerated .gamma.c expression on their CD8+, but not on their CD4+, T cells. IL-4, IL-7, and IL-15, which do not promote AICD, did not influence FasL or .gamma.c expression. These data provide evidence that IL-2 preps. CD8+ T lymphocytes for AICD by at least two mechanisms: 1) by up-regulating a pro-apoptotic mol., FasL, and 2) by down-regulating a survival mol., .gamma.c.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L68 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:433062 BIOSIS
DOCUMENT NUMBER: BA94:85187
TITLE: PERIPHERAL **DELETION** OF MATURE **CD8** -POSITIVE ANTIGEN-SPECIFIC T CELLS AFTER IN-VIVO EXPOSURE TO MALE ANTIGEN.
AUTHOR(S): ZHANG L; MARTIN D R; FUNG-LEUNG W-P; TEH H-S; MILLER R G
CORPORATE SOURCE: ONTARIO CANCER INSTITUTE, 500 SHERBOURNE STREET, TORONTO, ONTARIO, CAN. M4X 1K9.
SOURCE: J IMMUNOL, (1992) 148 (12), 3740-3745.
CODEN: JOIMA3. ISSN: 0022-1767.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB It has been well established that T cell tolerance to self Ag occurs primarily via clonal deletion of immature thymocytes in the thymus. Evidence also exists that there are additional mechanisms operative on mature T cells for establishing and maintaining tolerance in the periphery. To follow the fate of mature Ag-specific T cells in vivo, we used female transgenic mice, which contain a large population of male H-Y Ag-specific T cells that can be identified by immunostaining with mAb directed against CD8 and the transgenic TCR. H-Y Ag was introduced into these mice by injecting Ag-bearing male lymphocytes using conditions known to induce CTL precursor response reduction. The number of Ag-reactive CD8+ transgenic T cells in the periphery started to decrease after 2 days of in vivo exposure to male Ag. Decline was maximum (up to 80% of total) by 7 days, and stayed at this level for at least 6 wk. CD4+ cells and those CD8+ cells that did not carry the transgenic TCR were not affected. Most or all of the remaining Ag-reactive CD8+ cells in the periphery were fully responsive when stimulated by male Ag in vitro. Maturation of transgenic T cells in the thymus of injected mice remained the same as that of control animals. Our data provide direct evidence that mature Ag-reactive **CD8**+ cells are susceptible to clonal **deletion** in the periphery when exposed to the Ag in vivo. These findings suggest the presence of two types of APC (e.g., macrophages and dendritic cells) required for initiating an active immune response; and functionally deleting APC (or veto cells) capable of deleting mature T lymphocytes that recognize Ag presented on their surface. Functionally deleting APC that present self Ag to peripheral T cells may provide a fail-safe mechanism against autoreactive cells that escaped depletion during differentiation in the thymus.

L68 ANSWER 10 OF 11 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 92329348 MEDLINE
DOCUMENT NUMBER: 92329348 PubMed ID: 1385722
TITLE: **Peripheral tolerance** through clonal **deletion** of mature CD4-**CD8**+ T cells.
AUTHOR: Carlow D A; Teh S J; van Oers N S; Miller R G; Teh H S
CORPORATE SOURCE: Department of Microbiology, University of British Columbia, Vancouver, Canada.
SOURCE: INTERNATIONAL IMMUNOLOGY, **(1992 May)** 4 (5) 599-610.
Journal code: 8916182. ISSN: 0953-8178.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920904
Last Updated on STN: 19920904
Entered Medline: 19920819

AB Transgenic mice bearing the alpha beta transgenes encoding a defined T cell receptor specific for the male (H-Y) antigen presented by the H-2Db class I MHC molecule were used to study mechanisms of **peripheral tolerance**. Female transgenic mice produce large numbers of functionally homogeneous CD8+ male antigen-reactive T cells in the thymus that subsequently accumulate in the peripheral lymphoid organs. We have used three experimental approaches to show that male reactive CD8+ T cells can be eliminated from peripheral lymphoid organs after exposure to male antigen. (i) In female transgenic mice that were neonatally tolerized with male spleen cells, male reactive CD8+ T cells continued to be produced in large numbers in the thymus but were virtually absent in the lymph nodes. (ii) Injection of thymocytes from female transgenic mice into female mice neonatally tolerized with the male antigen, or into normal male mice, led to the specific elimination of male-reactive CD8+ T cells in the lymph nodes. (iii) Four days after male lymphoid cells were injected intravenously into female transgenic mice, male antigen-reactive CD8+ T cells recovered from the lymph nodes of recipient mice were highly apoptotic when compared to CD4+ (non-male reactive) T cells. These data indicate that tolerance to extrathymic antigen can be achieved through elimination of mature T cells in the peripheral lymphoid organs.

L64 ANSWER 7 OF 21 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2000015195 MEDLINE
DOCUMENT NUMBER: 20015195 PubMed ID: 10545998
TITLE: Requirement for T-cell apoptosis in the induction of peripheral transplantation tolerance.
AUTHOR: Wells A D; Li X C; Li Y; Walsh M C; Zheng X X; Wu Z; Nunez G; Tang A; Sayegh M; Hancock W W; Strom T B; Turka L A
CORPORATE SOURCE: Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
CONTRACT NUMBER: AI34665 (NIAID)
AI37691 (NIAID)
AI37798 (NIAID)
SOURCE: NATURE MEDICINE, **(1999 Nov)** 5 (11) 1303-7.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119

AB The mechanisms of allograft tolerance have been classified as deletion, anergy, ignorance and suppression/regulation. Deletion has been implicated in central tolerance, whereas peripheral tolerance has generally been ascribed to clonal anergy and/or active immunoregulatory states. Here, we used two distinct systems to assess the requirement for T-cell deletion in peripheral tolerance induction. In mice transgenic for Bcl-xL, T cells were resistant to passive cell death through cytokine withdrawal, whereas T cells from interleukin-2-deficient mice did not undergo activation-induced cell death. Using either agents that block co-stimulatory pathways or the immunosuppressive drug **rapamycin**, which we have shown here blocks the proliferative component of interleukin-2 signaling but does not inhibit priming for activation-induced cell death, we found that mice with defective passive or active T-cell apoptotic pathways were resistant to induction of transplantation tolerance. Thus, deletion of activated T cells through activation-induced cell death or growth factor withdrawal seems necessary to achieve peripheral tolerance across major histocompatibility complex barriers.

L9 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1998143744 MEDLINE
DOCUMENT NUMBER: 98143744 PubMed ID: 9485202
TITLE: Hepatocytes induce functional activation of naive CD8+ T lymphocytes but fail to promote survival.
AUTHOR: Bertolino P; Trescol-Biemont M C; Rabourdin-Combe C
CORPORATE SOURCE: Ecole Normale Superieure de Lyon, UMR 49, France.. P.Bertolino@centenary.usyd.edu.au
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Jan) 28 (1) 221-36.

Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980319

AB Intraperitoneal peptide injection of TCR-transgenic mice or expression of antigen in hepatocytes leads to an accumulation in the liver of specific **apoptotic CD8**+ T cells expressing activation markers. To determine whether liver cells are capable of directly activating naive CD8+ T cells, we have studied the ability of purified hepatocytes to activate TCR-transgenic CD8+ T cells in vitro. We show that hepatocytes which do not express CD80 and CD86 co-stimulatory molecules are able to induce activation and effective proliferation of specific naive CD8+ T cells in the absence of exogenously added cytokines, a property only shared by professional antigen-presenting cells (APC). Specific T cell proliferation induced by hepatocytes was comparable in magnitude to that seen in response to **dendritic** cells and was independent of **CD4**+ T cell **help** or bystander professional APC co-stimulation. During the first 3 days, the same number of divisions was observed in co-cultures of CD8+ T cells with either hepatocytes or splenocytes. Both APC populations induced expression of early T cell activation markers and specific cytotoxic T lymphocyte (CTL) activity. However, in contrast to T cells activated by splenocytes, T cells activated by hepatocytes lost their cytolytic function after 3 days of co-culture. This correlated with death of activated T cells, suggesting that despite efficient activation, proliferation and transient CTL function, T cells activated by hepatocytes did not survive. Death could be prevented by adding antigen-expressing splenocytes or exogenous IL-2 to the co-culture, indicating that hepatocytes are not involved in direct killing of CD8+ T cells but rather fail to promote survival. Dying cells acquired a CD8(low) TCR(low) B220+ phenotype similar to the one described for apoptotic intrahepatic T cells, suggesting an alternative model to account for the origin of these cells in the liver. The importance of these findings for the understanding of peripheral tolerance and the ability of liver grafts to be accepted is discussed.

L68 ANSWER 3 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 1999079087 MEDLINE
DOCUMENT NUMBER: 99079087 PubMed ID: 9862094
TITLE: CD4+ T cells orchestrate both amplification and **deletion** of **CD8**+ T cells.
AUTHOR: Frasca L; Piazza C; Piccolella E
CORPORATE SOURCE: Department of Cellular and Developmental Biology, La Sapienza University of Rome, Italy.
SOURCE: CRITICAL REVIEWS IN IMMUNOLOGY, **(1998)** 18 (6) 569-94. Ref: 221
Journal code: 8914819. ISSN: 1040-8401.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 19990324
Last Updated on STN: 19990324
Entered Medline: 19990308

AB This review focuses on the role of CD4+ T cells in regulating immune responses, orchestrating both the amplification and **deletion** of immune cells, particularly **CD8**+ T cells. These two functions, which represent only an apparent contradiction, appear to be two faces of the same process of regulation. In fact, because the immune response, once activated, needs to be carefully controlled or switched off when the antigenic stimulus is eliminated, the immune system has developed several strategies either to regulate clonal amplification or to avoid useless expansion of activated cells. In particular, we have reported many data demonstrating that CD4+ T cells may be indicated as the regulatory element in the activation as well as the **deletion** of **CD8**+ T cells. New data are also reported on the ability of anergic CD4+ T cells to suppress CD8+ T-cell activation through induction of **apoptosis**, and on the need for **CD8**+ T cells for antigen recognition in inducing cell death in CD4+ T cells. Moreover, the central role of CD4+ T cells in the maintenance of **peripheral tolerance** has been widely described.

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